effective dosages of trichothecenes inhaled per cigarette can be determined by using equipment developed in prior art for testing tar and nicotine content inhaled per cigarette or using glass fiber filters and pumps (emulating human inhalation patterns from cigarettes) and measurement of collected dosages could be performed after extraction with 90% aqueous methanol as described in Sorensen et. al. The appropriate number of cigarettes to be smoked to deliver the desired therapeutically effective dosages would then be determined.

Dose Determination:

Fig. 1A and 1B show the hyperactive protein synthesis inhibiting dose profile of roridin A and satratoxin G, respectively. Both roridin A and satratoxin G are macrocyclic trichothecenes. By ~ 5 ng/ml both had inhibited almost 100% of the hyperactive protein synthesis. Both did not reduce cell viability at concentrations of 10 ng/ml or less.

Figure 2A and 2B show the hyperactive protein synthesis inhibiting dose profile of T-2 and DAS, respectively. Both T-2 and DAS are simple trichothecenes. By doses of 5 ng/ml both had inhibited ~ 99% of hyperactive protein synthesis. Neither reduced cell viability at concentrations up to 200 ng/ml.

The hyperactive protein synthesis inhibiting profiles were constructed from data collected from in vitro experiments using human epidermoid cells, virally infected with HSV-2 to induce a hyperactive state of protein synthesis, and conducted and reported by Okazaki et. al. in the attached Journal of Agricultural and Biological Chemistry articles.

Conversion of in vitro concentrations to dosages required to achieve in vivo concentrations would be performed by simple mathematical methods. As an example, if a patients has an average lung weight of ~ 1200 grams and one desires to achieve a 5 ng/ml concentration of Satratoxin one would need to administer ~ 6,000 ng of dry satratoxin (i.e. 1 gram = 1 ml, 1200 gram lungs ~ 1200 ml, 1200 ml X 5 ng/ml = 6,000 ng.) by inhalation methods described above. Adjustments would be made for individual lung size differences and additional tumor mass where applicable.

Inhibitory, Cytotoxic, and Toxic doses are used in various treatment applications discussed later in the application. Using the data from the viral protein synthesis inhibiting model referenced above, dose guidelines for use in the Inhibitory, Cytotoxic, and Toxic embodiments of present invention are listed below in TABLE 1 and TABLE 2. Since no reduction in cell viability was observed at concentrations of less than 10 ng/ml for the two macrocyclic trichothecenes and 200 ng/ml for the two simple trichothecenes, TABLE 3 was constructed assuming two worst case scenarios 1) that none of the inhaled trichothecene is retained by the lungs and instead all of it finds its way to the roughly 42 liters of extracellular water outside the vasculature in the body or 2) more seriously the entire dose is accidentally injected directly into the blood stream which contains roughly 5 liters. TABLE 3 displays the maximum amount of trichothecene, in ng, that would not reduce cell viability systemically under the two scenarios. The maximum locally toxic doses for use in TABLE 2 are taken from TABLE 3.

TABLE 1: Trichothecene in Vitro Concentrations (in ng/ml)

	Inhibitory				Cytotoxic		Toxic
	50%	80%	90%	99%	Min	Max	Lo
Roridin A	1.4	2.0	3.3	5.0	6	10	11
Satratoxin	1.5	2.4	3.9	5.0	6	10	11
T-2	1.6	3.5	4.3	5.0	6	200	201
DAS	2.3	4.0	4.5	5.0	6	200	201

TABLE 2: In Vivo Dose for Average 1200 Gram Lungs (in ng)

	Inhibitory				Cytotoxic		Toxic	
	50%	80%	90%	99%	Min	Max	Lo	Hi
Roridin A	1680	2400	3960	6000	7200	12000	13200	50000
Satratoxin	1800	2880	4680	6000	7200	12000	13200	50000
T-2	1920	4200	5160	6000	7200	240000	241200	1000000
DAS	2760	4800	5400	6000	7200	240000	241200	1000000

lethality by inhalation. AMRIID computed the LD50 (lethal dose to 50% of people) by inhalation as 1,210 μg/kg of body weight. This translates to a 84,700,000 ng dose of T-2 being inhaled by a 70 kg person to have a 50% chance of mortality. This contrasts with the 6000 ng maximum inhibitory dose (~ 14,116 times smaller) for T-2, or the 240,000 maximum cytotoxic dose for T-2 (353 times smaller), or the 1,000,000 maximum toxic dose (85 times smaller) as proposed by present invention in the dose determination section of this application.

Cytotoxic Activity

The cytotoxic mechanisms of action against cancer cells are disclosed by applicant in U.S. Pat. # 6,342,520 for Locally Injectable Chemotherapeutics from column 4 line 29 to the end of column 7, and incorporated herein by reference.

Administration intervals for cytotoxic regimens using trichothecene are different from any prior art administration regimens. Prior art methods administer chemotherapeutics on 7 or 21 day intervals to allow recovery from systemic cytotoxicity, especially hematologic toxicity. Since localized administration of trichothecenes does not result in systemic toxicity, prior art administration intervals have no relevance to present invention. What is relevant for computing the frequency of administration of cytotoxic doses in present invention is the amount of time it takes any surviving cancer cells to inactivate the trichothecenes (i.e. by converting them to apotrichothecenes) plus approximately 8 hours to reassemble their cell cycle control machinery and start cycling again. Methods of computing administration frequency are disclosed by applicant in U.S. patent 6,342,520 from column 13 line 4 to line 53, incorporated herein by reference. Because of the genetic variability in mutation profiles, the preferred method of determining frequency of administration is by using frequent PET scans and positron emitting glucose to precisely determine when the cancer cells have inactivated the trichothecene and started cycling again, as described in U.S. Patent 6,342,520.